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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): HOWARD L. **WEINER** *et al.*

Serial No.: 08/279,275 Examiner: P. Achutamurthy

Filed: July 22, 1994 Group Art Unit: 1816

For: **TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION OF AUTOANTIGENS**

DECLARATION OF PROF. DR. KLAUS TOYKA

KLAUS V. TOYKA hereby declares:

1. I am a University Professor and Chairman in the Department of Neurology at the Bayerische Julius-Maximilians-Universität in Würzburg, Germany. My specialty is neuroimmunology. I have been involved with research and treatment of neurological autoimmune disorders including multiple sclerosis, and myasthenia gravis, polyneuritis and polymyositis for more than 20 years. I am also familiar with the literature in the field of neurological autoimmune disorders and am an author of more than 160 publications on the subject of autoimmunity. My qualifications are set forth in greater detail in my curriculum vitae attached as Exhibit 1.

2. I am not a co-inventor of the above identified application and I am not employed by the owner of the application. At the request of the applicant, I have reviewed the Campbell *et al.*, Whitacre *et al.*, and Nagler-Anderson *et al.* references which I understand have been applied to reject the claims in this application. I have also reviewed the results of clinical studies conducted by the inventors and described in the article attached as Exhibit 2.

3. It is my opinion that the oral tolerization of human patients described in this patent application and in the human trials described in annexed Exhibit 2 represents a meaningful and unexpected advance in the study of autoimmune diseases and in the treatment of MS. It is my understanding that the human trials I reviewed were conducted according to teachings in the patent application. These data show that myelin of which a major constituent is myelin basic protein (MBP) was orally administered to patients afflicted with the relapsing/remitting form of multiple sclerosis (MS). Of the patients receiving placebo in the study 12 out of 15 had MS attacks. Of the patients receiving oral MBP in the study, only 6 out of 15 suffered attacks of MS. Furthermore, there was a decrease in MBP reactive cells in the subjects fed myelin as compared to the placebo fed subjects and there was no evidence of toxicity or worsening of disease in the MBP-fed patients.

4. In my opinion these oral tolerization method results in humans were not suggested or described by the literature prior to 1987, when I understand the patent applica-

tion was filed. My opinion is explained in more detail below, and is based on my knowledge of autoimmune diseases and their treatment, including particularly multiple sclerosis, and on my review of the specification and other materials described herein.

5. It is my opinion that a person of ordinary skill in the field of autoimmune disease would find that the present invention is new and nonobvious, in comparison to the prior art Whitacre, Nagler-Anderson and Campbell.

6. The Whitacre Abstract reports on administration of MBP to animals which were subsequently immunized with MBP to induce experimental autoimmune encephalitis (EAE). In my opinion, those skilled in the art of neuroimmunology and autoimmune diseases, in 1986 or 1987, would not have sought to orally administer MBP to humans based on the teachings in the Whitacre reference, alone or considered together with the Campbell and Nagler-Anderson references. It is also my opinion that skilled practitioners, including researchers, clinicians and physicians, would not have extrapolated from the animal data of the Whitacre Abstract or the other references to the treatment of MS in humans, and would not have expected MBP to be suitably or successfully applied to human MS patients. The reasons for this are as follows.

7. In 1986/1987, those skilled in the fields of neuroimmunology and autoimmune diseases understood that there was a strong possibility that oral administration of myelin basic protein (MBP) to an individual afflicted with multiple sclerosis could actually worsen the patient's condition. This could occur

because it was thought that individuals afflicted with multiple sclerosis would likely already have been sensitized to the autoantigen responsible for the disease. Although it was not known for certain the MBP was the autoantigen responsible for MS, this was suspected to be the case. Hence, those skilled in the field did not turn to MBP as a treatment option. On the contrary, it was feared that oral administration of MBP could result in a heightened autoimmune reaction that would be seriously detrimental to patients. In short, it was believed that MBP could make the patient worse, not better. There was no expectation that MBP would work to alleviate MS in humans, despite reported animal experiments, such as those of Whitacre.

8. As early as 1977 I discussed the issue of oral tolerization with several colleagues in North America and Europe. Our discussions at that time related to the use of oral tolerization for possible treatment of myasthenia gravis, an autoimmune disease for which the responsible autoantigen was already known at the time. My colleagues and I hesitated to use oral tolerization for treatment of myasthenia gravis because we were afraid that such treatment would worsen the disease rather than treating it. Accordingly, I never made any use of oral tolerization for the treatment of myasthenia gravis, nor to my knowledge did any of the individuals with whom I had discussed the matter.

9. In the mid-1980s, I and many of my colleagues discussed the possible use of oral tolerization in other neuroimmunologic disorders including multiple sclerosis and polyneuritis. In both diseases, the antigen to which the immune

response is mounted was unknown. The various putative antigens, including myelin basic protein and other molecules, were not used by me or other experts in this field to treat these disorders because of our fear that such treatment would worsen the diseases in question. The work with animal models, such as the brief report in Whitacre, did not encourage me or my colleagues to apply oral tolerance to humans as a way to treat autoimmune diseases. We did not expect that chronic autoimmune diseases could be successfully treated by oral tolerance, or that human MS patients in particular could be treated by oral administration of MBP.

10. Oral administration of myelin basic protein also was not used to treat multiple sclerosis in 1986 or 1987, because at that time it was known that patients afflicted with multiple sclerosis have defects in their ability to generate immune suppression. Thus, even if an autoantigen was orally administered to such patients, the autoantigen may not have triggered the suppression response necessary to dampen the subject's autoimmune response. Because of this defect in suppression, such administration ran the risk of further sensitization, which would not treat the disease and could aggravate the patient's condition.

11. The teachings in the Campbell, Whitacre and Nagler-Anderson references would not have led those skilled in the field of autoimmune disease to experiment with the use of myelin basic protein in the treatment of multiple sclerosis. First, there was a fear of worsening the disease, as discussed

above. Second, there are significant differences between the animal models disclosed in Whitacre and Nagler-Anderson and human patients that are afflicted with an autoimmune disease, and particularly multiple sclerosis.

12. In the animal model, laboratory rats are fed the same autoantigen that is used to experimentally induce acute allergic encephalitis (EAE). Although experimental autoimmune EAE is somewhat akin to MS, and is useful for research, it is not the same disease in the same host and was not expected to behave in the same way. The same can be said of collagen-induced arthritis (CIA) a rodent model for rheumatoid arthritis (RA). Additionally, the animal model is based on the prevention or suppression of an acute condition that is artificially induced in the animal. In other words, unlike the human patient, the animal (in Whitacre and Nagler-Anderson) is not suffering from a chronic disease, has not been sensitized prior to administration of the autoantigen, and does not have an abnormal, compromised, or suppressed immune system associated with chronic autoimmune disease. This is quite different from a human patient afflicted with a chronic autoimmune condition such as multiple sclerosis. Here, the patient has been sensitized to the autoantigen over a long period of time -- even before the clinical manifestation of the disease -- and is afflicted with a chronic condition which is not easily reversed.[1]

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[1] Nagler-Anderson, which reports that feeding collagen after immunization is ineffective in suppressing collagen-induced arthritis, supports the view that oral tolerization would not be (continued...)

13. Under the circumstances, the suppression or prevention of an artificially induced surrogate disease in Lewis rats (EAE) was not readily transferable to the treatment of a chronic and therapy-resistant disease in humans (MS). Given the state of the art and the literature in 1986/87, there was no expectation that oral administration of MBP could be successfully used to treat MS in humans.

14. It should also be noted that the animal model employed by Whitacre et al. and similar models employed prior to 1987, did not address concerns about immunosuppression and sensitivity in human patients suffering from a persistent chronic disease. The models are directed to an acute autoimmune episode induced in laboratory animals, where sensitivity and immunosuppression of the kind observed in humans did not arise. Thus, the animal model and animal results were not readily transferable to humans. Moreover, the animal model had no bearing on the very real concern that oral administration of an autoantigen to humans (such as MBP for MS) would do more harm than good. In my opinion, a person of ordinary skill at the pertinent time would not have applied the Whitacre animal model to humans, because of the very real obstacles to successful treatment of humans which are not reflected in the animal model or the Abstract. These obstacles were and are well known to practitioners. In fact, it has been my personal experience that practitioners with knowledge

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[1](...continued)
effective in humans. Patients who develop autoimmune diseases, such as MS and RA, in fact suffer from an immune disorder long before clinical manifestation of the disease.

of the EAE animal model actually did not apply or transfer that model to humans. To the best of my knowledge, only the inventors of this application did so, despite the serious obstacles at the time.

15. In my opinion, results of animal experiments based on oral administration of MBP were not seen as transferable to humans because of significant limitations of the animal models. The risk of aggravated oral sensitization and immunosuppression in humans outweighed any desire to try oral MBP in humans. Thus, serious obstacles to the successful oral administration of MBP to humans were present, because of the fear that patients could actually be made worse by such treatment.

16. The Whitacre Abstract states that the results described "suggest that oral administration of MBP induces a state of antigen-specific unresponsiveness, which could be of value in establishing therapeutic protocols or multiple sclerosis." In my opinion, this was not an indication to skilled practitioners that oral administration of MBP can be successfully applied to humans afflicted with MS. This is so for the reasons given above, and in addition because the autoantigen for MS was not known. (MBP is a known autoantigen for EAE in rats, but was a suspected autoantigen in human MS.) This is another important difference between the animal model and human MS, which makes the invention in the application unexpectedly beneficial to patients. Since the autoantigen for MS was unknown, a person of ordinary skill in the field would not have taken the Abstract as any indication of a successful human therapy. Moreover, discussion

of future avenues for research are routine in abstracts of this kind, as is the hope that animal data might lead to more fruitful research in humans. Such statements, in my opinion, and in the context of the state of the art in autoimmune diseases in 1987, do not mean that the human therapy of the application is derivable from the Abstract. In my opinion, the successful oral use of MBP for MS patients according to the present application, and as demonstrated by clinical studies, was not predictable from the Abstract with any reasonable expectation of success, and provides a favorable therapeutic benefit.

17. The publication by Campbell reports on 64 human subjects afflicted with multiple sclerosis who were treated parenterally with human MBP for the stated purpose of testing it as a therapy in multiple sclerosis. Human myelin containing MBP was obtained from human brain and administered by intramuscular injection. The Campbell study has long been recognized in the field as extremely poorly designed and poorly conducted. The sole assessment was subjective: questionnaires answered by the patients, a notoriously unreliable practice. Moreover, the authors admitted (at p. 13 right col. and again at p. 14 left col.) that the questionnaires varied in wording and content, and they realized that the information provided in one questionnaire was not comparable with that of other questionnaires for the same patient. According to the reference, none of the patients were examined or assessed directly by a qualified physician (the sole examinations were only to verify that no new disease entity had arisen: p. 14 right col.), and no objective grading system was

employed (such as the Expanded Disability Status Scale). No attempt was made to randomize the patients who received myelin therapy or those who received placebo. There was considerable variability among the subjects as to both age and condition. All these glaring weaknesses were apparent to those skilled in the field even in 1974. The authors themselves recognized some of the weaknesses of their approach (Comments, pp. 14-15).

18. Thus, the study design and conduct of the Campbell clinical trial were far below the standard of a controlled clinical trial that was accepted by me and those skilled in the art of neuroimmunology and multiple sclerosis in the 1980's. In 1987, this trial design would in my opinion not have passed Internal Review Boards and Ethics Committees because of the foregoing multiple draw backs.[2] The study provides no clear indication that the tested treatment was promising. The results of Campbell et al. were in fact disregarded by the multiple sclerosis research and clinical community. To the best of my knowledge, no one followed up this study not even with synthetic fragments of MBP (which Campbell et al. suggested and which would have been free of the danger of infection). It would take what we know today, after the work described in the present patent

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[2] In addition, the authors knowingly took unreasonable and unethical risks in injecting patients with human myelin at a time when they knew not only about the danger of sensitization but also either knew or should have known about the high risk of infecting patients with infectious PRION material which is the putative agent of the deadly Creutzfeld-Jacob disease (known in 1974 as "slow viral disease"). Although this practice by the authors is not germane to the subject at hand, it is consistent with the poor quality of their research.

application and after the clinical work done by the Weiner group, to ascribe, post-hoc, any significance to the results reported by Campbell.

19. For the reasons outlined above, it is my opinion, based on my experience with autoimmune diseases, in the field of clinical immunology, and in treating patients with multiple sclerosis for more than 20 years, that those skilled in the art in 1986/87 would not have employed the teachings in the Whitacre Abstract or any other animal models regarding administration of MBP or another autoantigen to animals afflicted with EAE in trying to treat human patients afflicted with MS by administering to such patients MBP via the oral route. The teachings in the Campbell publication using MBP via the intramuscular route in patients with MS is to be criticized for the severe weaknesses in the study design, and the unconvincing clinical observations. Therefore, those skilled in the art in 1986/87 would not have employed the teachings by Campbell in combination with those of Whitacre and/or Nagler-Anderson for the treatment of multiple sclerosis, whatever the route of administration of the antigen.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may

jeopardize the validity of the application or any patent issuing thereon.

2 Oct 96
DATE

PROF. DR. KLAUS V. TOYKA

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Prof. Dr. K. V. Toyka

CURRICULUM VITAE

15 April 1945	born in Biberach, Germany
1950 - 1964	Primary School and High School education (including the equivalent to Junior College)
1964 - 1970	Medical School education at the University of Munich Medical Doctorate Thesis in Endocrinology
1970	U.S. Examination for Foreign Medical Graduates
1971	Medical Licensure
1971 - 1974	Residency at the Munich University Hospitals in Internal Medicine and Pediatric Neurology
1974 - 1976	Clinical and Research Fellow in Neuromuscular Diseases at the Johns Hopkins Medical Institutions, Baltimore, USA
1976 - 1979	Residency in Neurology and since 1978 Lecturer (Junior Faculty) Dept. of Neurology, Technical University, Munich
1979 - 1981	Tenured Associate Professor of Neurology, University of Düsseldorf. Head of the Neuroimmunology and Neuromuscular Labs.
1981 - 1989	Professor and Vice-Chairman, Department of Neurology, University of Düsseldorf
1989 to present	Professor and Chairman, University of Würzburg
Memberships	New York Academy of Sciences (1976), American Academy of Neurology (1986), American Neurological Association (1988), International Society of Neuroimmunology (1988), German Societies of Neurology, Muscular Dystrophy, and Physiology (1978), European Neurological Society

Honors and Awards	Award of the Myasthenia Gravis Foundation, U.S.A., Heinrich-Pette-Award of the German Neurological Society, President, Advisory Board of the German MS Society, Honorary Corresponding Member, Belgian Neurological Society, Named Lectureships Associate Editor and Member of the Editorial Board of International Science Journals

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